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(54) Title: ORAL MUCOSAL DOSAGE FORMS OF APOMORPHINE

(57) Abstract: A pharmaceutical formulation for the prolonged-release oral mucosal administration of apomorpine which comprises a therapeutically effective amount of apomorphine or a pharmaceutically acceptable salt or pro-drug thereof in combination with a carrier comprising from about 10 percent by weight to about 95 percent by weight dextran, based upon the total weight of the formulation. In one embodiment of the invention, dextran having a molecular weight in the range between about 5000 Daltons and 100,000 Daltons is the sole component of the formulation for prolonging the release of the active drug component. In an alternative embodiment, a mixture of microcrystalline cellulose and dextran act as the components to prolong the release of apomorphine.

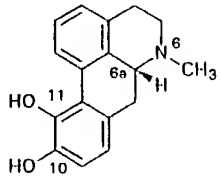
Oral Mucosal Dosage Forms of Apomorphine

Technical Field

The present invention relates to pharmaceutical formulations suitable for the administration of a therapeutic agent *via* oral mucosal tissue. More particularly, the present invention concerns tablet dosage forms containing dextran which are particularly suited for prolonged release delivery of apomorphine through oral mucosal tissue.

Background of the Invention

The compound (*R*)-5,6,6a,7-tetrahydro-6-methyl-(4*H*)-benzo[*de,g*]-quinoline-10,11-diol, known generically as apomorphine, was the first dopamine receptor agonist to be synthesized. It is derived from morphine by treatment with hydrochloric acid (L. Small, *et al.*, J. Org. Chem., 5:334 (1940)) or by heating morphine in the presence of zinc chloride (Mayer, Ber., **4**: 171 (1871)). The compound has the structure:



possessing a chiral center at position 6a. The total synthesis of the racemic mixture was reported by J. L. Neumeyer, *et al.*, J. Pharm. Sci., 59: 1850 (1970), and the synthesis of the separate *R*- and *S*-enantiomers by V. J. Ram and J. L. Neumeyer, J. Org. Chem., 46: 2830 (1981). The compound possesses a basic nitrogen atom at position 6 and is thus capable of existing in both the free base form as well as in acid addition salt forms.

Apomorphine has a high affinity for D_2, D_3, and D_4 receptors, and is unique in its affinity for D_1 receptors. It elicits effects similar to those of levodopa and, as such, has been widely used as a treatment for Parkinson's disease. Apomorphine, in higher doses, is a strong emetic, and has been used for a number of years as an agent to induce emesis. More recently its use, at

appropriate doses, has been suggested for treating dementia (United States Patent 5,744,476), Parkinsonism (United States Patent 4,970,200), damage to the central nervous system (United States Patent 4,742, 054), and male (United States Patents 5,985,889; 5,770,606; and 5,624,677) and female (United States Patent 5,945,117) sexual dysfunction, as well as an agent for enhancing ocular development (United States Patents 5,360,801; and5,284,843),

Administration of apomorphine by oral ingestion is thwarted by its high first-pass hepatic metabolism. As a consequence, formulations or devices for various alternative routes of administration of apomorphine have been taught in the literature, including transdermal (United States Patents 5,985,317; 5,939,094; 5,562,917; 4,837,027; 4,806,341; 4,781,924; and 4,645,502), sublingual or buccal (United States Patents 5,888,534; 5,624,677; and 5,770,606), intranasal (United States Patent 5,756,483), and parenteral (United States Patents 5,024,998; and 4,983,586). Although most dosage formulations for apomorphine, other than parenteral formulations, are currently under development, a pen injection system for self-administration of apomorphine by Parkinsonism patients is commercially available from Britannia Pharmaceuticals Limited, 41-51 Brighton Road, Redhill, Surrey RH1 6YS, England. Formulations including complexes of apomorphine with cyclodextrin (United States Patents 5,742,954; and 5,324,718) are also known.

United States Patents 5,624,677 and 5,888,534 describe a controlled-release tablet formulation for the sublingual or buccal administration of apomorphine (cf. Prior Art Example below). The formulation comprises a mixture of a water-insoluble carrier forming a porous structure which is filled, coated, or covered by the active ingredient, an osmotic agent, and a water dispersible polymer, with the mixture being compressed into tablets. Upon exposure to biological fluids such as saliva, and with the assistance of the osmotic agent, the release of apomorphine is controlled by the competing actions of the water-insoluble carrier and the water-dispersible polymer. Both components undergo changes, with swelling of the water-insoluble carrier

providing additional surface area with attendant channeling and fluid penetration. This leads, in the absence of competing influences, to faster diffusion or release of the active ingredient. At the same time however, gelling of the water-dispersible polymer slows the release of the active agent from the tablet matrix. Balancing of the competing effects of the water-insoluble carrier and the water-dispersible polymer by judicious formulation, results in the desired apomorphine release profile when the tablet is held under the tongue.

As suitable swellable hydrophilic carriers, the patents teach the use of ethyl cellulose, fumed silica, cross-linked poly(vinylpyrrolidone), microcrystalline cellulose, silica, dicalcium phosphate, and calcium carbonate. Suitable osmotic agents taught by the patents are mannitol, sorbitol, lactose, glucose, fructose, sucrose, mono- and disaccharides, glycerin, polyelectrolytes, urea, sodium chloride, potassium chloride, and other inorganic and organic salts. Suitable polymers include hydroxypropyl cellulose, hydroxymethyl cellulose, gelatin, carboxymethyl cellulose, gum tragacanth, gum acacia, agar gum, sodium alginate, poly(methacrylic acid) poly(acrylic acid), salts of poly(silicic acid), poly(lactic acid), water soluble starch, carbomers, polycarbophils, poly(vinyl alcohol), poly(ethylene glycol), alkoxy block copolymers, methyl cellulose, polysorbates, and poly(maleic acid).

United States Patent 5,770,606 describes compressed tablets for sublingual administration of apomorphine which comprise apomorphine hydrochloride, mannitol, ascorbic acid, citric acid, microcrystalline cellulose(Avicel® PH102), hydroxypropyl methyl cellulose (Methocel® E4M), aspartame, and magnesium stearate. Alternative formulations which are taught replace the microcrystalline cellulose and hydroxypropyl methyl cellulose with β-cyclodextrin or hydroxypropyl-β-cyclodextrin.

Summary of the Invention

The present invention provides a pharmaceutical formulation for the prolonged-release oral mucosal administration of apomorphine which

comprises a therapeutically effective amount of apomorphine or a pharmaceutically acceptable salt or pro-drug thereof in combination with a carrier comprising from about 10 percent by weight to about 95 percent by weight dextran, based upon the total weight of the formulation. In one embodiment of the invention, dextran having a molecular weight in the range between about 5000 Daltons and 100,000 Daltons is the sole component of the formulation for prolonging the release of the active drug component. In an alternative embodiment, a mixture of microcrystalline cellulose and dextran act as the components to prolong the release of apomorphine.

Brief Description of the Drawing Figure

In the drawing, Figure 1 is a graph showing the dissolution profiles for direct compression tablets of the prior art and three examples of the present invention.

Detailed Description

As used throughout this specification and the appended claims, the following terms have the meanings ascribed to them in the following definitions.

The term "prodrug" refers to compounds that are rapidly transformed *in vivo* to yield apomorphine, as for example, by hydrolysis in blood. T. Higuchi and V. Stella provide a thorough discussion of the prodrug concept in "Prodrugs as Novel Delivery Systems," Vol. 14 of the A.C.S. Symposium Series, American Chemical Society (1975). Examples of esters useful as prodrugs for compounds containing carboxyl groups may be found on pages 14-21 of *Bioreversible Carriers in Drug Design: Theory and Application*, edited by E.B. Roche, Pergamon Press (1987).

The term "prodrug ester group" refers to any of several ester-forming groups that are hydrolyzed under physiological conditions. Examples of prodrug ester groups include pivoyloxymethyl, acetoxymethyl, phthalidyl, indanyl and methoxymethyl, as well as other such groups known in the art.

As used herein, the term "pharmaceutically acceptable ester" refers to esters which hydrolyze in vivo and include those that break down readily in the human body to leave the parent compound or a salt thereof. Suitable ester groups include, for example, those derived from pharmaceutically acceptable aliphatic carboxylic acids, particularly alkanoic, alkenoic, cycloalkanoic and alkanedioic acids, in which each alkyl or alkenyl moiety advantageously has not more than 6 carbon atoms. Examples of particular esters includes formates, acetates, propionates, butryates, acrylates and ethylsuccinates.

As used herein, the term "pharmaceutically acceptable salt" refers to those salts which are within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, allergic response and the like, and are commensurate with a reasonable benefit/risk ratio. Pharmaceutically acceptable salts are well known in the art. For example, S. M. Berge, et al. describe pharmaceutically acceptable salts in detail in J. Pharmaceutical Sciences, 66: 1-19 (1977), incorporated herein by reference. The salts can be prepared in situ during the final isolation and purification of the compounds of the invention, or separately by reacting the free base function with a suitable organic acid. Examples of pharmaceutically acceptable, nontoxic acid addition salts are salts of an amino group formed with inorganic acids such as hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid and perchloric acid or with organic acids such as acetic acid, oxalic acid, maleic acid, tartaric acid, citric acid, succinic acid or malonic acid or by using other methods used in the art such as ion exchange. Other pharmaceutically acceptable salts include adipate, alginate, ascorbate, aspartate, benzenesulfonate, benzoate, bisulfate, borate, butyrate, camphorate, camphorsulfonate, citrate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, formate, fumarate, glucoheptonate, glycerophosphate, gluconate, hemisulfate, heptanoate, hexanoate, hydroiodide, 2-hydroxy-ethanesulfonate, lactobionate, lactate, laurate, lauryl sulfate, malate, maleate, malonate, methanesulfonate, 2-naphthalene-

sulfonate, nicotinate, nitrate, oleate, oxalate, palmitate, pamoate, pectinate, persulfate, 3-phenylpropionate, phosphate, picrate, pivalate, propionate, stearate, succinate, sulfate, tartrate, thiocyanate, p-toluene-sulfonate, undecanoate, valerate salts, and the like. Representative alkali or alkaline earth metal salts include sodium, lithium, potassium, calcium, magnesium, and the like. Further pharmaceutically acceptable salts include, when appropriate, nontoxic ammonium, quaternary ammonium, and amine cations formed using counterions such as halide, hydroxide, carboxylate, sulfate, phosphate, nitrate, loweralkyl sulfonate and aryl sulfonate. The preferred salt of apomorphine for use in the formulations of the present invention is the hydrochloride.

By the term "oral mucosal administration" of a pharmaceutical formulation of the present invention is meant the delivery of the drug contained in the formulation through the mucosal tissue located in the oral cavity of a mammal including the tongue, roof of the mouth, inner cheeks (buccal) and under the tongue (sub-lingual).

The term "prolonged-release" formulation means a formulation which achieves the slow release of the active drug component in the formulation over an extended period of time.

"Dextrans" are highly branched glucosans (glucose polymers) produced by the fermentation of sucrose solutions by certain bacteria including *Leuconostoc mesenteroides* and *Betacoccus arabinosaceus*. Dextrans having 90 percent of the molecules in the molecular weight range of 50,000 to 100,000 Daltons, prepared by the partial hydrolysis of native dextran, have been used as plasma extenders in the treatment of shock caused by the loss of body fluids. Dextrans have been given by infusion as a pre-, per- and post-operative plasma and blood replacement, in the prophylaxis of venous thrombosis and pulmonary embolism, and in the improvement of microcirculation. Dextrans of a number of different molecular weight ranges are commercially available.

Dextrans suitable for use in the pharmaceutical formulations of the present invention have average molecular weights ranging from about 5000

Daltons to about 100,000 Daltons, with preferred dextrans having average molecular weights in the range of between about 9000 Daltons to about 70,000 Daltons. Particularly preferred dextrans for use in the formulations of this invention are those having average molecular weights (determined by gel filtration) of about 9500 Daltons, 37,500 Daltons, and 69,000 Daltons, respectively, available from Pharmacia Biotech, 800 Centennial Ave. 1327 Piscataway, NJ 08855-1327 designated as grades PM10, PM 40 and PM70, respectively.

In one embodiment, the pharmaceutical formulations of the present invention contain, in addition to the active drug component, one or more grades (i.e. average molecular weights) of dextran as the sole polymeric component for controlling the prolonged release of the drug. In such cases, the amount of dextran in the formulation ranges from about 80 percent by weight to about 95 percent by weight dextran, based upon the total weight of the formulation. Alternatively, the component for controlling the prolonged release of the active drug may be a mixture of microcrystalline cellulose and dextran. In this alternative embodiment, the microcrystalline cellulose comprises up to about 25 weight percent, preferably up to about 20 weight percent of the formulation. When microcrystalline cellulose and dextran make up the components which control the release of the active drug component, the dextran comprises from about 5 weight percent to about 15 weight percent of the total weight of the formulation, preferably about 10 weight percent. A filler, makes up for the decreased amount of dextran in the dextran/microcrystalline cellulose formulations, and may comprise from about 10 to about 60 weight percent of the total formulation weight. of the composition. Suitable diluents, when needed in the formulations of the present invention include dicalcium phosphate, calcium sulfate, lactose, mannitol, cellulose, kaolin, sodium chloride, dry starch, and powdered sugar. The preferred diluent in the formulations of this invention is mannitol.

The formulations may also contain typical binders, lubricants, disintegrants, and coloring, sweetening, and flavoring agents well known to

practitioners of the pharmaceutical formulation arts. Suitable sweetening agents include sugars, as well as sugar substitutes including aspartame, acesulfame potassium salt, and saccharin. The sugar substitutes are preferred since they impart adequate sweetness to the formulation without taking up much bulk in the formulation, as would be the case with natural sugars. When present in the formulation of the present invention, one or more sugar substitutes is present as a sweetener in amounts ranging between about 1 percent to about 5 percent, preferably about 2 percent, based upon the total weight of the formulation.

Suitable lubricants, utilized in amounts ranging between about 1%and 5% by weight of the total formulation include sodium benzoate, mixtures of sodium benzoate and sodium acetate, sodium chloride, leucine, Carbowax 4000, magnesium stearate, mixtures of magnesium stearate and sodium lauryl sulfate, and magnesium lauryl sulfate. A preferred lubricant in formulations of the present invention is magnesium stearate.

A preferred dosage form of the present invention is a direct compression tablet containing from about 2 to about 10 weight percent apomorphine or a pharmaceutically acceptable salt or pro-drug thereof per tablet, together with a carrier comprising dextran. A particularly preferred unit dosage form of the present invention is a 100 mg tablet containing between about 2 to10 mg of apomorphine hydrochloride. Direct compression tablets are prepared as detailed in the examples given below.

Slow release of apomorphine to the subject is achieved by oral mucosal administration of the tablet. That is, the tablet is held in the mouth, either on or below the tongue, or against the inner cheek until the tablet has dissolved and the drug is absorbed through the mucosal tissue into the blood stream. The oral mucosal administration of apomorphine permits direct delivery to the blood stream and obviates the elimination of the drug by first pass hepatic metabolism which would otherwise result from ingestion of the tablet. The prolonged release of apomorphine, brought about by the presence of dextran prevents the initial rapid rise of apomorphine serum concentration with its

attendant undesirable nausea side effects, and ensures effective serum levels over a longer period. The formulations of the present invention contain significantly reduced amounts of microcrystalline cellulose or, in one embodiment of the invention, no microcrystalline cellulose. Thus, the unwanted "gritty" feeling left by this tablet component after dissolution in the mouth is greatly reduced or eliminated.

For purposes of illustration, the following Examples present formulations of the alternative embodiments of the present invention. Examples 1-3 illustrate tablet formulations of apomorphine in which reduced amounts of microcrystalline cellulose are combined with dextrans of varying molecular weights. Examples 4 and 5 illustrate formulations in which dextrans of different molecular weights are employed as the sole polymeric component for prolonging the release of the active drug component. For purposes of comparison, prior art and control formulations are also presente

Prior Art Examples

Formulation	Microcrystalline Cellulose (mg/Tablet)	Table Weight (mg)	Microcrystaline Cellulose (% by Weight)
A	22.70	60.00	37.83
B	22.70	60.00	37.83
C	22.70	60.00	37.83
D	40.00	105.00	38.09
E	40.00	100.00	40.00
F	40.00	105.00	38.09
G	40.00	105.00	38.09
H	40.00	105.00	38.09
I	40.00	105.00	38.09
J	40.00	105.00	38.09
K	40.00	105.00	38.09
L	40.00	105.00	38.09
M	40.00	103.00	38.83
N	40.00	103.00	38.83
O	40.00	107.00	37.38
P	40.00	105.00	38.09
Q	40.00	103.20	38.75

In each of the formulations listed above, microcrystalline cellulose comprises at least 37.4% of the total weight of each tablet. Since microcrystalline cellulose typically contains about 20% by weight of particles having an average particle size greater than 100 μM, this means that each tablet contains appreciable amounts of this larger particle size water insoluble material which imparts a gritty sensation upon dissolution of the tablet in the mouth.

Control Example A

2 mg Apomorphine Tablet Formulation

Ingredient	mg/Tablet	% of Tablet
Apomorphine hydrochloride, USP	2.06	2.06
Mannitol, USP	62.44	62.44
Microcrystalline cellulose, NF	20.00	20.00
Hydroxypropyl methylcellulose (Methocel® E4M Premium)	10.00	10.00
Entrapped cool mint orange (WONF)	2.00	2.00
Acesulfame K	2.00	2.00
Magnesium stearate	1.50	1.50
Totals	100.00	100.00

Control Example B

2 mg Apomorphine Tablet Formulation

Ingredient	mg/Tablet	% of Tablet
Apomorphine hydrochloride, USP	2.06	2.06
Mannitol, USP	66.54	66.54
Microcrystalline cellulose, NF	20.00	20.00
Citric acid, anhydrous, USP	3.50	3.50
Ascorbic acid, USP	0.20	0.20
Edetate disodium dihydrate	0.10	0.10
Colloidal silicon dioxide	0.10	0.10
Synthetic red iron oxide	2.00	2.00
Entrapped cool mint orange (WONF)	2.00	2.00
Acesulfame K	2.00	2.00
Magnesium stearate	1.50	1.50
Totals	100.00	100.00

Example 1

2 mg Apomorphine Tablet Formulation

Ingredient	mg/Tablet	% of Tablet
Apomorphine hydrochloride, USP	2.06	2.06
Mannitol, USP	56.54	56.54
Microcrystalline cellulose, NF	20.00	20.00
Dextran 10	10.00	10.00
Citric acid, anhydrous, USP	3.50	3.50
Ascorbic acid, USP	0.20	0.20
Edetate disodium dihydrate, USP	0.10	0.10
Colloidal silicon dioxide	0.10	0.10
Synthetic red iron oxide	2.00	2.00
Entrapped cool mint orange (WONF)	2.00	2.00
Acesulfame K	2.00	2.00
Magnesium stearate	1.50	1.50
Totals	100.00	100.00

Example 2

2-mg Apomorphine Tablet

Ingredient	mg/Tablet	% of Tablet
Apomorphine hydrochloride, USP	2.06	2.06
Mannitol, USP	56.54	56.54
Microcrystalline cellulose, NF	20.00	20.00
Dextran 40	10.00	10.00
Citric acid, anhydrous, USP	3.50	3.50
Ascorbic acid, USP	0.20	0.20
Edetate disodium dihydrate, USP	0.10	0.10
Colloidal silicon dioxide	0.10	0.10
Synthetic red iron oxide	2.00	2.00
Entrapped cool mint orange (WONF)	2.00	2.00
Acesulfame K	2.00	2.00
Magnesium stearate	1.50	1.50
Totals	100.00	100.00

Example 3

2-mg Apomorphine Tablet

Ingredient	mg/Tablet	% of Tablet
Apomorphine hydrochloride, USP	2.06	2.06
Mannitol, USP	56.54	56.54
Microcrystalline cellulose, NF	20.00	20.00
Dextran 70	10.00	10.00
Citric acid, anhydrous, USP	3.50	3.50
Ascorbic acid, USP	0.20	0.20
Edetate disodium dihydrate, USP	0.10	0.10
Colloidal silicon dioxide	0.10	0.10
Synthetic red iron oxide	2.00	2.00
Entrapped cool mint orange (WONF)	2.00	2.00
Acesulfame K	2.00	2.00
Magnesium stearate	1.50	1.50
Totals	100.00	100.00

Example 4

2-mg Apomorphine Tablet

Ingredient	Mg/Tablet
Apomorphine HCl, USP	2.06
Dextran 40 (first portion)	10.00
Dextran 40 (second portion)	20.00
Dextran 40 (third portion)	62.44
Entrapped Cool Mint Orange (WONF)	2.00
Acesulfame K	2.00
Magnesium Stearate, NF	1.50
Total	100.00

Example 5

2-mg Apomorphine Tablet

Ingredient	Mg/Tablet
Apomorphine HCl, USP	2.06
Dextran 70 (first portion)	10.00
Dextran 70 (second portion)	20.00
Dextran 70 (third portion)	62.44
Entrapped Cool Mint Orange (WONF)	2.00
Acesulfame K	2.00
Magnesium Stearate, NF	1.50
Total	100.00

Examples 4 and 5 were prepared by dry mixing the first portion of dextran, the apomorphine hydrochloride, the flavoring agent (entrapped cool mint orange), and the sweetener (Acesulfame K). This mixture was then passed through a 20 mesh sieve (0.033 inch, 0.84 mm nominal opening). The second portion of dextran was then passed through a 20 mesh sieve and added to the mixture of active ingredient, flavoring agent, sweetener, and first portion of dextran. The third portion of dextran was similarly sized through a 20 mesh sieve, added to the previous mixture of ingredients, and dry mixed for twenty minutes. The resulting powdered mixture was compressed into 100 mg tablets using a standard one-quarter inch (0.64 cm) concave tableting die. The Control Example and Examples 1-3 were similarly prepared, with additional mixing steps to accommodate the additional ingredients.

Table 1 presents the physical and dissolution properties for tablets prepared in accordance with the various examples. Hardness was measured by the conventional method using the Schleuniger hardness tester (cf. "Remington's Pharmaceutical Sciences," 18th Edition., A. R. Gennaro, Ed., Mack Publishing Co., 1990, pp. 1639-1640). Dissolution rates were measured using the standard USP No. 1 dissolution apparatus (*op cit.*, pp. 595-596.). Tablets were placed in the basket and stirred at 50 rpm at a temperature of 37°C ± 0.5°C. At times 10, 20, 30 and 45 minutes after the starting time, 10 mL aliquot samples were removed and analyzed for apomorphine content. The results of these measurements are presented in Table 1 and depicted graphically in Figure 1.

Table 1

Example	Tablet Hardness (kPascals)	Tablet Dissolution Rate (% Dissolved)			
		10 Min.	20 Min.	30 Min	45 Min.
Control B		103.1	---	---	---
1	3.7	43.3	70.5	90.4	97.7
2	4.2	40.6	64.9	84.4	100.0
3	4.3	34.8	56.8	84.3	97.0
4	2.2	10.9	22.1	33.7	46.4
5	1.1	12.3	24.4	34.5	43.8

Control Example B illustrates a formulation which was devoid of any polymer ingredient which would function to prolong the release of apomorphine. As a consequence, the drug was essentially completely released within the first ten minutes. In the case of apomorphine such a formulation would administer a "bolus" dose of the drug causing, in some patients, serum levels of the dug to rise above the threshold required to induce nausea. This is, of course, undesirable and a slower release is needed. Such prolonged release formulations are presented in Examples 1-5. The data for Examples 1-3 show, for example, complete or almost complete release of apomorphine over a period of 45 minutes.

Figure 1 shows release profiles for Examples 1-3 in comparison with a prior art matrix tablet formulation lacking dextran, but containing a mixture of microcrystalline cellulose and hydroxypropyl methylcellulose as the drug-release controlling ingredients. As can be seen by examining Figure 1, the drug release profiles for Examples 1-3 of the present invention more closely approach linearity than does the profile for the prior art formulation. The release of apomorphine from the formulations of Examples 4 and 5, containing dextran as the only polymeric component, were likewise prolonged, reaching 46.4% and 43.8%, respectively at the end of 45 minutes. Thus, formulations containing only dextran or a mixture of dextran and reduced levels of

microcrystalline cellulose can be "tailor-made" to achieve the desired dissolution profile.

The stabilities toward oxidative darkening of tablets formulated in accordance with of Examples 4 and 5 of the present invention were compared to the stability of tablets formulated in accordance with Control Example A. None of the three formulations contained antioxidants such as ascorbic or citric acid. The tablets were placed in an open glass vial and allowed to stand in a lighted room for a period of ten days at 70°C. The appearance of the tablets at the end of the ten days was recorded, using a subjective scale which ranged from zero to ten. A value of zero was assigned if no change was observed in the appearance of the tablets after ten days; a value of ten corresponded to a complete change in appearance at the end of ten days. All appearance values were assigned comparison with control samples of the tablet formulations kept in sealed vials at ambient temperature in a darkened room. The results are presented in Table 2.

Table 2

Formulation Stability

Example	Appearance After 10 Days
Control A	Dark 4, medium gray, moderate speckling
4	Dark 2, light gray, slight speckling
5	Dark 2, light gray, slight speckling

The data in Table 2 show that compressed apomorphine tablets containing dextran undergo less oxidative degradation over time than similarly compressed tablets which lack dextran and contained the prior art matrix of microcrystalline cellulose and hydroxypropyl methylcellulose. While some darkening of the dextran-containing tablets was observed, this may be countered by addition of small amounts of antioxidants in addition to the dextran, as in Examples 1-3 above. Prior art sublingual tablet formulations containing apomorphine and a matrix of microcrystalline cellulose and hydroxypropyl methylcellulose teach the inclusion of from about 4.67 to about

8.33 weight percent of a mixture of ascorbic and citric acids. In contrast, the dextran-containing formulations of the preset invention contain less than about 3.7 weight percent of the two acids.

The formulations of the present invention thus provide a prolonged-release means for delivering apomorphine by oral mucosal administration which provide a number of advantages. The formulations achieve the desired release profile with fewer ingredients, resulting in savings; the formulations possess increased stability toward oxidative degradation without comparatively high levels of antioxidants; and the formulations are comparatively free of the gritty feeling produced in the mouth by large-particle ingredients employed in prior art matrix tablet formulations.

The Examples given above are presented for illustrative purposes only and should not be read as limiting the scope of the present invention as it is defined by the specification and the appended claims.

WE CLAIM:

1. A pharmaceutical formulation comprising a therapeutically effective amount of apomorphine or a pharmaceutically acceptable salt or prodrug thereof in combination with a carrier comprising from about 10 percent by weight to about 95 percent by weight dextran, based upon the total weight of the formulation.

2. The pharmaceutical formulation according to Claim 1 wherein said dextran has an average molecular weight in the range between about 5000 Daltons and about 100,000 Daltons.

3. A pharmaceutical formulation according to Claim 2 wherein said dextran has an average molecular weight in the range between about 9500 Daltons and about 69,000 Daltons.

4. A pharmaceutical formulation according to Claim 1 wherein said carrier comprises from about 80 percent by weight to about 95 percent by weight dextran, based upon the total weight of the formulation.

5. A pharmaceutical formulation according to Claim 1 wherein said carrier comprises from about 5 weight percent to about 15 weight percent dextran and up to about 25 weight percent microcrystalline cellulose, all percentages based upon the total weight of the formulation.

6. The pharmaceutical formulation according to Claim 1 wherein said pharmaceutically acceptable salt of apomorphine is the hydrochloride salt.

7. The pharmaceutical formulation according to Claim 5 further comprising from about 10 percent by weight to about 60 percent by weight mannitol.

8. A tablet dosage form for the oral mucosal administration of apomorphine comprising from about 2 mg to about 10 mg of apomorphine or a pharmaceutically acceptable salt or prodrug thereof in combination with a carrier comprising from about 10 to about 95 mg of dextran.

9. A tablet dosage form according to Claim 8 wherein said dextran has an average molecular weight in the range of between about 5000 Daltons and about 100,000 Daltons.

10. A tablet dosage form according to Claim 9 wherein said dextran has an average molecular weight in the range between about 9500 Daltons and about 69,000 Daltons.

11. A tablet dosage form according to Claim 8 wherein said carrier comprises from about 80 percent by weight to about 95 percent by weight dextran, based upon the total weight of the tablet.

12. A tablet dosage form according to Claim 8 wherein said carrier comprises from about 5 weight percent to about 15 weight percent dextran and up to about 25 weight percent microcrystalline cellulose, all percentages based upon the total weight of the tablet.

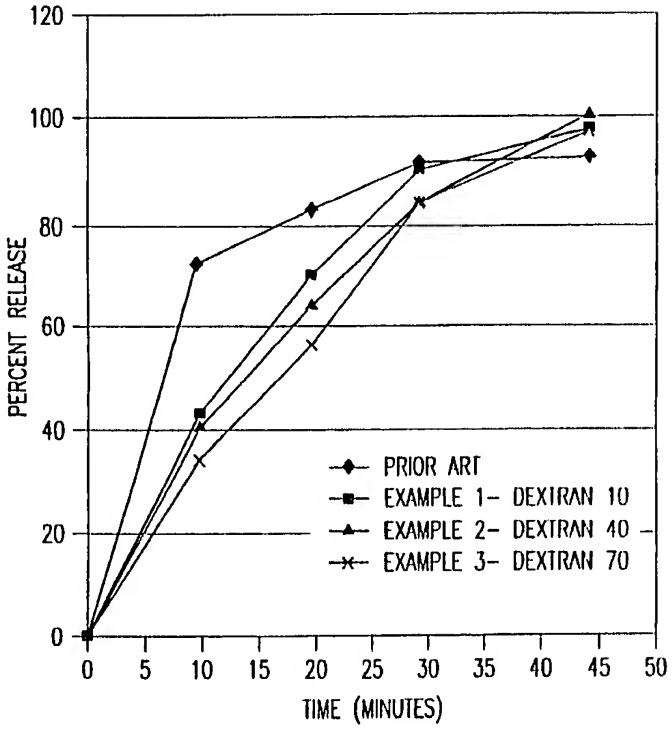


FIG.1

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 00/34548

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/485 A61K9/20 A61K9/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
WPI Data, PAJ, EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 94 22445 A (MERKUS, FRANCISCUS) 13 October 1994 (1994-10-13) claims 11,12,16,17 page 9; example 1C	1-7
X	WO 97 06786 A (SCHERER) 27 February 1997 (1997-02-27) claims 1,4 page 7, line 16 - line 24 page 8, line 2 - line 15	1,6

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
26 April 2001	11/05/2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Ventura Amat, A

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 00/34548

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9422445 A	13-10-1994	BE 1006870 A	10-01-1995
		BE 1006871 A	10-01-1995
		BE 1006872 A	10-01-1995
		AU 6428894 A	24-10-1994
		EP 0689438 A	03-01-1996
		EP 0865789 A	23-09-1998
		JP 8508472 T	10-09-1996
		US 5942251 A	24-08-1999
		US 5756483 A	26-05-1998
WO 9706786 A	27-02-1997	AT 196249 T	15-09-2000
		AU 709641 B	02-09-1999
		AU 6750996 A	12-03-1997
		BG 102254 A	30-10-1998
		BR 9610424 A	30-03-1999
		CA 2229597 A	27-02-1997
		CZ 9800455 A	15-07-1998
		DE 69610323 D	19-10-2000
		DE 69610323 T	22-02-2001
		DK 850050 T	16-10-2000
		EP 0850050 A	01-07-1998
		ES 2151672 T	01-01-2001
		HU 9900183 A	28-05-1999
		JP 11511162 T	28-09-1999
		NO 980669 A	17-04-1998
		NZ 315740 A	29-06-1999
		PL 324988 A	06-07-1998
		PT 850050 T	31-01-2001
		SK 19198 A	09-09-1998
		ZA 9607032 A	04-03-1997

Form PCT/ISA/210 (patent family annex) (July 1992)